

Associations between the incidence of antiphosphatidylserine and antiphosphatidylethanolamine antibodies and clinical manifestations of systemic lupus erythematosus

Filip Butkiewicz, Michał Kaszuba, Michał Brzeziński, Jan Iżbicki, Marek Kubiś, Hubert Łopiński, Michał Borowiak, Michał Szelepajło, Katarzyna Fischer, Jacek Fliciński

Department of Rheumatology and Internal Diseases, Pomeranian Medical University, Szczecin, Poland

KEY WORDS

antiphosphatidylethanolamine antibodies, antiphosphatidylserine antibodies, antiphospholipid antibodies, antiphospholipid syndrome, systemic lupus erythematosus

ABSTRACT

INTRODUCTION Antiphosphatidylethanolamine antibodies (aPE) and antiphosphatidylserine antibodies (aPS) belong to a group of antiphospholipid antibodies (aPL) that occur in patients with antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE).

OBJECTIVES The aim of this study was to examine associations between the elevated serum concentration of aPE/aPS, the clinical manifestations of SLE, and the presence of other autoantibodies.

PATIENTS AND METHODS The study group included 71 patients with SLE. The control group comprised 36 healthy volunteers. In both groups, serum aPS and aPE concentrations were measured with enzyme-linked immunosorbent assays. Clinical data, including clinical manifestations and the laboratory markers of SLE, were obtained from medical records.

RESULTS The study revealed a higher prevalence of aPE in patients with SLE than in controls (54.93% vs. 5.56%). aPS were observed in the study group less frequently compared with aPE (12.68% vs. 54.93%) and were absent in controls. Anticardiolipin antibodies and APS were found to be associated with the presence of aPS. Thrombocytopenia, Raynaud phenomenon, and myocardial infarction were observed more frequently among aPS-positive patients. The presence of aPE was also associated with the occurrence of mucosal ulcers in the mouth cavity. A positive correlation between aPS and erythrocyte sedimentation rate (ESR) was also observed. The serum concentration of aPE inversely correlated with red blood cell count and positively with ESR.

CONCLUSIONS The presence of aPS in patients with SLE is associated with thrombocytopenia, Raynaud phenomenon, and cardiac complications.

INTRODUCTION Antiphosphatidylethanolamine (aPE) and antiphosphatidylserine (aPS) antibodies belong to a group of antiphospholipid antibodies (aPL). Those heterogeneous autoreactive antibodies show affinity to anionic membrane phospholipids and phospholipid-binding plasma proteins.¹

aPL may induce clot formation similarly to phospholipids, including phosphatidylethanolamine and phosphatidylserine, which are

physiologically present in the lipid bilayer membrane of endothelial cells and platelets.² This phenomenon leads to thrombosis, thrombocytopenia, and obstetric complications commonly observed in antiphospholipid syndrome (APS).²⁻⁵

Although aPL are found in 1% to 5% of the general population, the prevalence of APS is said to be no more than 0.5%. APS is either associated with other diseases, most commonly with systemic

Correspondence to:
Filip Butkiewicz, MD, Klinika
Reumatologii i Chorób Wewnętrznych,
ul. Unii Lubelskiej 1, 71-252 Szczecin,
Poland, phone: +48-91-425-33-40,
fax: +48-91-425-33-44, e-mail:
fbbutkiewicz@gmail.com
Received: June 20, 2014.
Revision accepted:
September 10, 2014.
Published online:
September 15, 2014.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2014;
124 (11): 573-578
Copyright by Medycyna Praktyczna,
Kraków 2014

TABLE 1 Demographic data of the study group

Parameter	Study group (n = 71)	Controls (n = 36)	P value
mean age, y	44.3 ± 23.8	47.5 ± 27.5	0.4
age range, y	18–68	20–75	–
sex, n (%)			0.3
women	61 (85.9)	28 (77.8)	
men	10 (14.1)	8 (22.2)	
current smokers, n (%)	10 (14.1)	3 (8.3)	0.09
ex-smokers, n (%)	7 (9.9)	6 (16.7)	
nonsmokers, n (%)	51 (71.8)	11 (30.6)	

Data are presented as mean ± standard deviation or number (percentage).

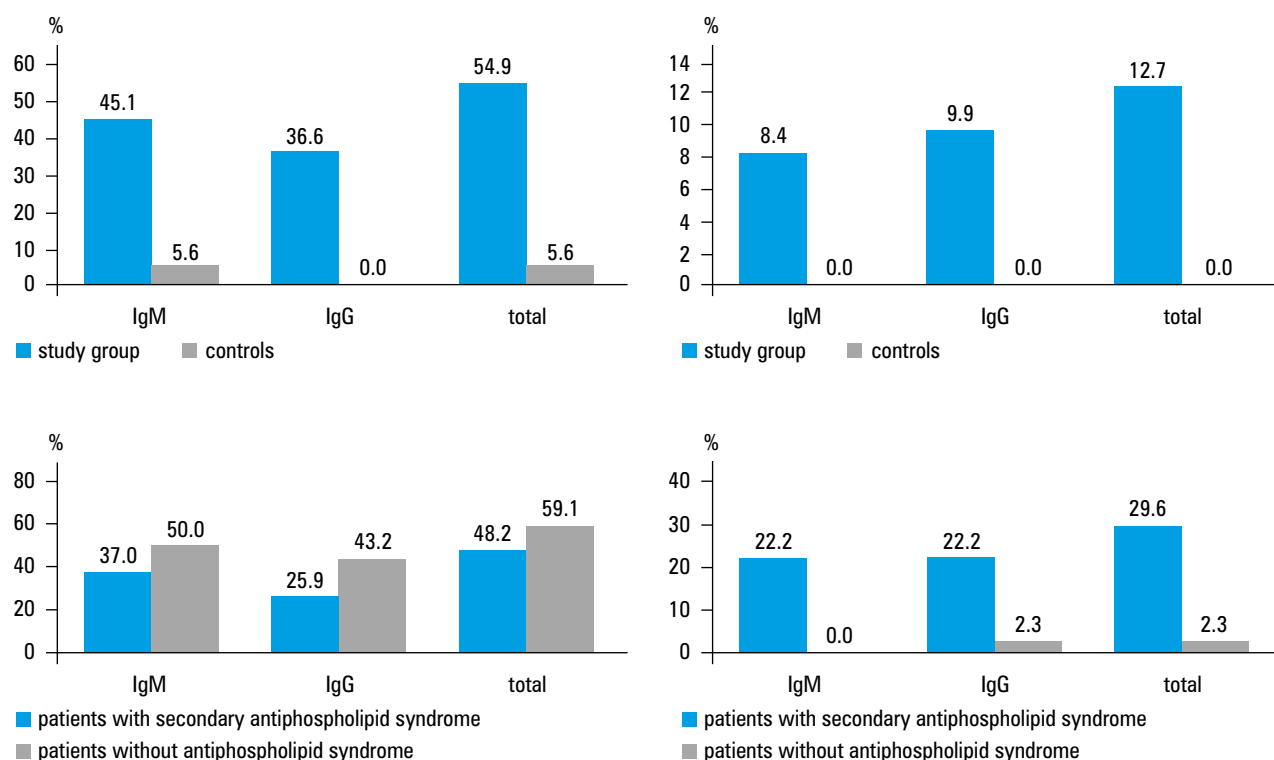


FIGURE Incidence of antiphosphatidylserine and antiphosphatidylethanolamine antibodies in controls and patients with systemic lupus erythematosus, with and without secondary antiphospholipid syndrome. Abbreviations: IgG – immunoglobulin G, IgM – immunoglobulin M

lupus erythematosus (SLE) or occur as a primary disorder.⁵ Moreover, it has been reported that aPL occur also in SLE patients without concomitant APS.^{2,3,6,7} Three types of aPL are considered most typical for APS: lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and anti-β₂-glycoprotein-1 (anti-β₂GPI) antibodies.⁵ Moreover, aCL and LAC are the most important predictive factors for thrombotic vascular occlusion in the course of APS.^{4,8–10} In patients with SLE and APS, aPS and aPE are observed less frequently compared with aCL. However, both aPS and aPE appear to act similarly to aCL.¹¹

The presence of aPL significantly increases the risk of thrombosis; however, the most distinctive clinical manifestations of SLE are related to antinuclear antibodies (ANA). Anti-double-stranded DNA antibodies (anti-dsDNA), closely associated with SLE, cross-react with small nuclear ribonucleoprotein and ribosomal P proteins. Antibodies to ribosomal P proteins are associated with neuropsychiatric, renal, and hepatic lupus involvement. Anti-La/anti-Ro autoantibodies

are typical for Sjögren syndrome, but they can also be observed in SLE patients. Anti-La/anti-Ro autoantibodies, present in a gravida, predispose the new-born child to neonatal lupus and congenital heart block. In addition to ANA, numerous other antibodies may occur in the course of SLE. Perinuclear antineutrophil cytoplasmic antibodies are present in 25% of SLE patients; however, contrary to anti-dsDNA, they do not correlate with disease activity.⁷

The aim of this study was to examine associations between the elevated serum concentration of aPE/aPS, the occurrence of SLE clinical manifestations, and the presence of other autoantibodies.

PATIENTS AND METHODS The study involved 71 patients with SLE and 36 volunteers. The inclusion criteria were as follows: age ≥18 years and diagnosis of SLE. All members of the study group met the American College of Rheumatology classification criteria for SLE from 1982 and 2012.^{12,13} The inclusion criteria for controls were

TABLE 2 Correlation between Systemic Lupus Erythematosus Disease Activity Index and antiphosphatidylserine and antiphosphatidylethanolamine antibodies concentrations

Antibody	Antibody class	<i>r</i>	<i>P</i>
aPS	IgM	−0.2	0.5
	IgG	0.05	0.8
aPE	IgM	−0.5	0.05
	IgG	−0.02	0.9

Abbreviations: aPE – antiphosphatidylethanolamine antibodies, aPS – antiphosphatidylserine antibodies, others – see [FIGURE](#)

as follows: age ≥ 18 years and no autoimmune diseases reported.

The study was approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin, Poland. All patients who participated in the study signed informed consent documents.

The exclusion criteria for the study and control groups were as follows: inability to obtain a blood sample (regardless of the cause), inability to understand the nature of the study, and lack of signed consent. No eligible patients refused to participate in the study.

Serum samples of all study participants were tested with a double-antibody enzyme-linked immunosorbent assay to determine aPS (DEMEDITEC Diagnostics GmbH, Kiel-Wellsee, Germany) and aPE (The Binding Site Inc., San Diego, United States) concentrations in immunoglobulin (Ig) M and IgG classes. The serum concentration of aPS/aPE of 10 IU/ml and higher was considered positive.

Medical records of all patients (from 1990–2010) were reviewed. Data on comorbidities, detected autoantibodies, treatment, clinical manifestations of SLE, and results of laboratory tests were collected. Smoking status and obesity were evaluated in terms of pack-years and body mass index, respectively. The administered treatment was evaluated in all SLE patients. The presence of the following autoreactive antibodies was verified: ANA, aCL, LAC, antiprothrombin antibodies (APTR), and anti- β_2 GPI. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was calculated. All SLEDAI descriptors were also evaluated separately.

In addition to SLEDAI descriptors, the following SLE manifestations were considered: cognitive disorders, emotional liability, peripheral nerve palsy, mononeuropathy, polyneuropathy, myasthenia gravis, ischemic heart disease (IHD), arterial and venous thrombosis, Raynaud phenomenon, interstitial pneumonia, pulmonary fibrosis, skin lesions, photosensitivity, and lupus nephritis. In all patients, the erythrocyte sedimentation rate (ESR), concentration of C-reactive protein (CRP), complete blood count, and echocardiogram were assessed.

Statistical analysis was performed using Pearson's χ^2 statistics, Spearman's rank correlation

coefficient, and logistic regression analysis. The statistical software package STATA 5.0 (Stata-Corp, College Station, United States) was used for all analyses. A *P* value of less than 0.05 was considered significant.

RESULTS No significant differences in demographic characteristics were found between the groups ([TABLE 1](#)). Except hypertension, no other diseases were present in the control group. In the study group, the prevalence of hypertension was higher compared with controls (43.7% vs. 5.0%; *P* = 0.001).

We observed a higher prevalence of aPE compared with aPS in the study group (54.9% vs. 12.7%). In the control group, aPE were detected less frequently and only in the IgM isotype. Of note, aPS were absent in controls ([FIGURE](#)).

Secondary APS was present in 27 of 71 patients (38%). In APS-positive subjects, aPS occurred more frequently when compared with patients without concomitant APS. Moreover, aPS in the IgM class were not observed in patients without secondary APS. Surprisingly, the prevalence of aPE was higher in the APS-negative group (59.1% vs. 48.2%) ([FIGURE](#)).

The presence of aPE was not related to the presence of ANA, aCL, LAC, APTR, and anti- β_2 GPI. Except in the relationship between aPS in the IgM class and aCL in the IgM class (odds ratio [OR], 7.45; 95% confidence interval [CI], 1.84–351.85; *P* = 0.009), the presence of aPS was not associated with the presence of other autoantibodies.

No significant differences were observed in the SLEDAI between aPS/aPE-positive and aPS/aPE-negative patients ([TABLE 2](#)).

Myocardial infarction occurred more often in subjects with a concentration of aPS in the IgM class of 10 IU/ml or higher (OR, 14.75; CI, 1.62–133.94; *P* = 0.02). Raynaud phenomenon (OR, 30.50; CI, 4.23–220.01; *P* = 0.001), and thrombocytopenia (OR, 7.20; CI, 1.39–37.19; *P* = 0.02) were also related to the presence of aPS in the IgM class. Mucosal ulcers were more common in aPE-positive patients (OR, 5.45; CI, 1.35–22.01; *P* = 0.02). The elevated concentration of aPE in the IgM class was associated with a significantly decreased risk of proteinuria (OR, 0.23; CI, 0.06–0.92; *P* = 0.04). Echocardiographic findings were not dependent on the presence of aPS or aPE ([TABLE 3](#)).

The concentrations of aPS in the IgM class (*r* = 0.4; *P* = 0.002) and aPE in the IgG class (*r* = 0.3; *P* = 0.03) correlated positively with ESR. A negative correlation was found between the aPE concentration in the IgM class and red blood cell count (*r* = −0.3; *P* = 0.01).

DISCUSSION The presence of aPS in healthy subjects as well as in patients with SLE and APS has already been reported.^{2,3,9,14} It has also been found that aPS occur more commonly in SLE patients, especially those with concomitant APS, compared with healthy controls. Furthermore, it has been

TABLE 3 Relationship between antiphosphatidylserine and antiphosphatidylethanolamine antibodies and complications of systemic lupus erythematosus

Parameter	Antibody	Class	Odds ratio	CI	P
myocardial infarction	aPS	IgM	14.75	1.62–133.94	0.02
Raynaud phenomenon	aPS	IgM	30.50	4.23–220.01	0.001
thrombocytopenia	aPS	IgG	7.20	1.39–37.19	0.02
mucosal ulcers	aPE	IgM	5.45	1.35–22.01	0.02
proteinuria	aPE	IgM	0.23	0.06–0.92	0.04

Abbreviations: CI – confidence interval, others – see [FIGURE](#) and [TABLE 2](#)

proved that aPS titer is usually higher in patients with SLE and APS.^{2,3,14}

Similarly, previous studies have shown a higher prevalence of aPE among patients with SLE and APS. However, aPE occurred in these patients more frequently than aPS.^{4,6} Our findings on the prevalence of aPS and aPE among patients with SLE and APS and healthy subjects are consistent with the previous studies.

In the present study, aPS often coexisted with aCL in patients with secondary APS. Previous studies have also revealed significant associations between aPS and aCL.^{2,3,15} We did not confirm the relationship between aPS and anti- β_2 GPI,^{7,15} and we did not observe any association with LAC.^{3,16}

Our results are generally in agreement with the previous studies in that we did not find any relationship between aPE and other aPL in SLE patients.¹⁷

A study by Caccavo et al.¹⁸ revealed no association between Raynaud phenomenon and aPL, including aPS.¹⁸ On the contrary, our findings showed that the presence of aPS in the IgM class considerably increases the risk of Raynaud phenomenon.

A study by Jafarzadeh et al.¹⁹ showed an elevated risk of IHD and myocardial infarction in aPS-positive subjects. Moreover, our previous study indicated a higher incidence of IHD in aPS-positive patients with SLE.²⁰ In the present study, the presence of aPS in the IgM class significantly increased the risk of myocardial infarction. However, aPS had no effect on the occurrence of IHD.

Recently, aPS has been included in the set of aPL used in the Global Anti-Phospholipid Syndrome Score, a new tool designed to quantitatively score the risk of thrombosis.²¹ However, the elevated incidence of thromboembolic complications previously reported in aPS-positive subjects was not observed in our study.^{21,22}

We did not confirm associations between echocardiographic findings and the presence of aPS^{17,23} or aPE^{4,24} revealed by previous research.

Unlike prior studies, no significant relationship was detected between the presence of aPS/aPE and the incidence of neurological disorders.^{9,25} Contrary to previous studies, the occurrence of lupus nephritis was not associated with the presence of aPS/aPE.^{26,27}

Our observations indicate that despite their high prevalence in SLE patients, aPS are weakly associated with SLE complications or do not have any considerable effect on the disease course. However, further studies in larger patient groups are needed to substantiate this hypothesis. Contrary to aPE, the presence of aPS seems to predispose patients to some SLE complications. In the present study, the number of SLE manifestations related to the presence of aPS was lower than expected.

In conclusion, the presence of aPS in SLE patients was found to be associated with thrombocytopenia, Raynaud phenomenon, and cardiac complications. Moreover, aPS commonly coexisted with APS and aCL. Although the prevalence of aPE is considerably higher in SLE patients, no significant association was found between aPE and the clinical manifestations of SLE. According to the present study, the occurrence of aPS predisposes subjects to some SLE complications, while aPE do not seem to have any considerable effect on the disease course. However, further studies are necessary to confirm these observations.

Contribution statement JF conceived the idea for the study. JF and FB contributed to the design of the research. All authors were involved in data collection. FB and MB analyzed the data. FB, MK, and JF edited and approved the final version of the manuscript. FB and MK prepared the manuscript for submission.

REFERENCES

- 1 Vlachoyiannopoulos PG, Samarkos M, Sikara M, Tsiligris P. Antiphospholipid antibodies: laboratory and pathogenetic aspects. *Crit Rev Clin Lab Sci*. 2007; 44: 271-338.
- 2 Sahin M, Duzgun N, Tunc SE, et al. Clinical manifestations and antiphosphatidylserine antibodies in patients with systemic lupus erythematosus: is there an association? *Clin Rheumatol*. 2007; 26: 154-160.
- 3 Szodoray P, Tarr T, Tumpek J, et al. Identification of rare anti-phospholipid/protein co-factor autoantibodies in patients with systemic lupus erythematosus. *Autoimmunity*. 2009; 42: 497-506.
- 4 Karmochkine M, Cacoub P, Piette JC, et al. Antiphosphatidylethanolamine antibody as the sole antiphospholipid antibody in systemic lupus erythematosus with thrombosis. *Clin Exp Rheumatol*. 1992; 10: 603-605.
- 5 Marchetti T, Cohen M, Gris JC, de Moerloose P. Diagnosis and management of obstetrical antiphospholipid syndrome: where do we stand? *Pol Arch Med Wewn*. 2013; 123: 713-720.
- 6 Conti F, Alessandri C, Soric M, et al. Thin-layer chromatography immunostaining in detecting anti-phospholipid antibodies in seronegative antiphospholipid syndrome. *Clin Exp Immunol*. 2012; 167: 429-437.
- 7 Alarcón-Segovia D, Cabral AR. Autoantibodies in systemic lupus erythematosus. *Curr Opin Rheumatol*. 1996; 8: 403-407.

- 8 Tsutsumi A, Hayashi T, Chino Y, et al. Significance of antiprothrombin antibodies in patients with systemic lupus erythematosus: clinical evaluation of the antiprothrombin assay and the antiphosphatidylserine/prothrombin assay, and comparison with other antiphospholipid antibody assays. *Mod Rheumatol*. 2006; 16: 158-164.
- 9 Kahles T, Humpich M, Steinmetz H, et al. Phosphatidylserine IgG and beta-2-glycoprotein I IgA antibodies may be a risk factor for ischaemic stroke. *Rheumatology (Oxford)*. 2005; 44: 1161-1165.
- 10 Staub HL, Harris EN, Khamashta MA, et al. Antibody to phosphatidylethanolamine in a patient with lupus anticoagulant and thrombosis. *Ann Rheum Dis*. 1989; 48: 166-169.
- 11 McIntyre JA, Wagenknecht DR. Anti-phosphatidylethanolamine (aPE) antibodies: a survey. *J Autoimmun*. 2000; 15: 185-193.
- 12 Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982; 25: 1271-1277.
- 13 Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012; 64: 2677-2686.
- 14 Radway-Bright EL, Ravirajan CT, Isenberg DA. The prevalence of antibodies to anionic phospholipids in patients with the primary antiphospholipid syndrome, systemic lupus erythematosus and their relatives and spouses. *Rheumatology (Oxford)*. 2000; 39: 427-431.
- 15 Palomo I, Pereira J, Alarcon M, et al. Antiphospholipid antibodies in Chilean patients with systemic lupus erythematosus. *J Lab Clin Med*. 2002; 140: 336-341.
- 16 Zuazu-Jausoro I, Oliver A, Monserrat I, et al. [Importance of antiphosphatidylserine antibodies in patients with lupus anticoagulant. Analysis of 30 cases]. *Med Clin (Barc)*. 1990; 95: 210-213. Spanish.
- 17 Amoroso A, Cacciapaglia F, De Castro S, et al. The adjunctive role of antiphospholipid antibodies in systemic lupus erythematosus cardiac involvement. *Clin Exp Rheumatol*. 2006; 24: 287-294.
- 18 Caccavo D, Del Porto F, Garzia P, et al. Raynaud's phenomenon and antiphospholipid antibodies in systemic lupus erythematosus: is there an association? *Ann Rheum Dis*. 2003; 62: 1003-1100.
- 19 Jafarzadeh A, Poorgholami M, Nemati M, et al. High serum levels of rheumatoid factor and anti-phosphatidylserine antibody in patients with ischemic heart disease. *Iran J Immunol*. 2011; 8: 34-44.
- 20 Ostanek L, Brzasko M, Fischer K, Płóńska E. [Antiphospholipid syndrome and antiphospholipid antibodies as a risk factors of ischaemic heart disease and myocardial infarction in patients with systemic lupus erythematosus]. *Pol Arch Med Wewn*. 2006; 115: 407-413. Polish.
- 21 Sciascia S, Sanna G, Murru V, et al. GAPSS: the Global Anti-Phospholipid Syndrome Score. *Rheumatology (Oxford)*. 2013; 52: 1397-1403.
- 22 Otomo K, Atsumi T, Amenugul O, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. *Arthritis Rheum*. 2012; 64: 504-512.
- 23 Ostanek L, Płóńska E, Peregud-Pogorzelska M, et al. [Cardiovascular abnormalities in systemic lupus erythematosus patients in echocardiographic assessment]. *Pol Merk Lek*. 2006; 117: 305-308. Polish.
- 24 Granel B, Serratrice J, Hubert AM, et al. [IGM hyperimmunoglobulinemia anti-phosphatidylethanolamine antibodies of the IgM isotype: clinical and biological study of 72 patients with immune disorders]. *Rev Med Interne*. 2000; 21: 595-598. French.
- 25 Syuto T, Shimizu A, Takeuchi Y, et al. Association of antiphosphatidylserine/prothrombin antibodies with neuropsychiatric systemic lupus erythematosus. *Clin Rheumatol*. 2009; 28: 841-845.
- 26 Fialová L, Zima T, Tesar V, et al. Antiphospholipid antibodies in patients with lupus nephritis. *Ren Fail*. 2003; 25: 747-758.
- 27 Gigante A, Gasperini ML, Cianci R, et al. Antiphospholipid antibodies and renal involvement. *Am J Nephrol*. 2009; 30: 405-412.

Związek między występowaniem przeciwciał przeciw fosfatydyloserynie i fosfatydyloetanololoaminie a manifestacjami klinicznymi toczenia rumieniowego układowego

Filip Butkiewicz, Michał Kaszuba, Michał Brzeziński, Jan Iżbicki, Marek Kubiś, Hubert Łopiński, Michał Borowiak, Michał Szelepajło, Katarzyna Fischer, Jacek Fliciński

Klinika Reumatologii i Chorób Wewnętrznych, Pomorski Uniwersytet Medyczny, Szczecin

SŁOWA KLUCZOWE

przeciwciała przeciw fosfatydyloetanololoaminie, przeciwciała przeciw fosfatydyloserynie, toczén rumieniowaty układowy, zespół antyfosfolipidowy

STRESZCZENIE

WPROWADZENIE Przeciwciała przeciw fosfatydyloetanololoaminie (aPE) i fosfatydyloserynie (aPS) należą do grupy przeciwciał antyfosfolipidowych (aPL), występujących u chorych z zespołem antyfosfolipidowym (*antiphospholipid syndrome* – APS) i toczniem rumieniowatym układowym (*systemic lupus erythematosus* – SLE).

CELE Celem pracy było zbadanie związku między podwyższonym stężeniem aPE/aPS w surowicy, a występowaniem manifestacji klinicznych SLE i obecnością innych autoprzeciwciał.

PACJENCI I METODY Grupę badaną stanowiło 71 chorych na SLE. Grupę kontrolną stanowiło 36 zdrowych ochotników. W obu grupach oznaczono stężenia aPS i aPE w surowicy metodą immunoenzymatyczną. Dane kliniczne, w tym manifestacje kliniczne i wskaźniki laboratoryjne SLE, uzyskano w oparciu o dokumentację medyczną.

WYNIKI Badanie wykazało większą częstość występowania aPE u pacjentów z SLE w porównaniu z grupą kontrolną (54,93% vs 5,56%). Ponadto aPS występowały rzadziej niż aPE w grupie badanej (12,68%), natomiast w grupie kontrolnej były nieobecne. Wykazano również związek między przeciwciałami antykar-diolipinowymi i APS, a obecnością aPS. U pacjentów z SLE, u których występowały aPS, zaobserwowano częstsze występowanie małopłytkowości, objawu Raynauda oraz zawału serca. Obecność aPE wiązała się z występowaniem nadżerek błony śluzowej jamy ustnej. Stwierdzono także dodatnią korelację pomiędzy aPS, a OB. Stężenie aPE korelowało ujemnie z liczbą czerwonych krwinek, a dodatnio z OB.

WNIOSKI Obecność aPS u chorych na SLE związana jest ze zwiększonym ryzykiem wystąpienia małopłytkowości, objawu Raynauda i powikłań sercowych.

Adres do korespondencji:
lek. Filip Butkiewicz, Klinika
Reumatologii i Chorób Wewnętrznych,
Pomorski Uniwersytet Medyczny,
ul. Unii Lubelskiej 1, 71-252 Szczecin,
phone: +48-91-425-33-40,
fax: +48-91-425-33-44,
e-mail: fbutkiewicz@gmail.com
Praca wpłynęła: 20.06.2014.
Przyjęta do druku: 10.09.2014.
Publikacja online: 15.09.2014.
Nie zgłoszono sprzeczności
interesów.
Pol Arch Med Wewn. 2014;
124 (11): 573-578
Copyright by Medycyna Praktyczna,
Kraków 2014